REMARKS

These remarks are responsive to the Office Action mailed May 8, 2009. Claims 1, 3, 4, 6 – 16, and 22 – 28 are pending. Claims 1, 3, 4, and 6 – 16 are under consideration, and claims 22 – 28 are withdrawn.

Reconsideration and withdrawal of the rejections made in the above-referenced Office Action are respectfully requested in view of the following remarks.

Election/Restrictions

The Office Action maintains the requirement for restriction with respect to claims 22 – 28, subject to rejoinder at the Examiner's discretion.

In response, Applicant respectfully requests reconsideration of the requirement for restriction and rejoinder of claims 22 – 28.

Claim Rejections – 35 U.S.C. § 103(a)

The Office Action maintains the rejection of claims 1, 3, 4, and 6 – 16 under 35 U.S.C. 103(a) as allegedly being unpatentable over Tanaka et al. (WO 97/02832; hereinafter TANAKA), in view of Yamahira et al. (U.S. Patent No. 4,244,943; hereinafter YAMAHIRA). In particular, the Office Action states that TANAKA teaches a lyophilized composition comprising hepatocyte growth factor, a stabilizer, sodium chloride, buffer, and a surface active agent. The Office further states that while TANAKA teaches that the stabilizing agent can include amino acids in general, TANAKA does not explicitly teach inclusion of arginine, lysine, histidine, glutamine, proline, glutamic acid, or aspartic acid as the stabilizing agent.

For this missing feature the Office relies upon YAMAHIRA, which teaches the lyophilization of urokinase using a combination of human serum albumin (HSA) with a polar amino acid such as arginine, aspartic acid, etc. The Office further alleges that it would have been obvious to one of ordinary skill in the art to modify the invention of TANAKA by selecting any of the polar amino acids taught by YAMAHIRA as stabilizing agents. The Office further alleges that "[t]he motivation to do so would be to choose an amino acid known to be effective in stabilizing lyophilized preparations." (Office Action dated September 19, 2008 at page 5, lines 3 – 5, and the Office Action dated May 8, 2009 at page 3, lines 24 – 25.)

Furthermore, in reply to Applicant's previous arguments, the Office Action concedes that "certain improved properties may in fact be present in the [instant] compositions comprising the specifically recited amino acids." (Office Action at page 4, lines 6 – 8.) However, the Office concludes that the claimed invention would be obvious over TANAKA in view of YAMAHIRA anyway, relying on the assertion that YAMAHIRA indicates that many of the amino acids recited in the claims are suitable as stabilizers in compositions comprising lyophilized proteins. Moreover, in response to YAMAHIRA's failure to disclose the use of polar amino acids with any protein other than urokinase, the Office asserts that "there is no reason to believe that the teachings of the [YAMAHIRA] patent, specifically which compounds are suitable for increasing stability of a lyophilized protein, are so limited as to only apply to this one particular protein." (Office Action at page 5, lines 8 – 11.) With regard to the concentration of HGF in the aqueous solution from which the claimed invention is prepared as compared to TANAKA, the Office Action asserts that "[a]bsent evidence that a product made from a higher concentration is patentably distinct, the limitation does not receive patentable weight." (Office Action at page 4, lines 23 – 24.)

In response, Applicant submits that the claimed invention is not unpatentable over TANAKA in view of YAMAHIRA. In particular, Applicant submits that the Office Action has misrepresented YAMAHIRA's teachings. For example, at column 1, lines 27 – 28, YAMAHIRA states that "a combination of HSA with a polar amino acid has *a specific* stabilizing effect on *urokinase*" (emphasis added). Moreover, at column 1, lines 52 – 54, YAMAHIRA states that the "specific effect [observed] . . . *cannot be observed with combinations of any other substances*" (emphasis added). YAMAHIRA further notes at column 1, lines 57 – 63, that "[t]he stabilization effect of the combination stabilizer of this invention can be specifically observed *only* in the combination of HSA and a polar amino acid or a salt thereof, and there *can not be observed* such a remarkable stabilizing effect as above even in the combination of HSA with other optional non-polar amino acid, such as for example, cysteine, leucine, methionine and the like" (emphasis added). These statements are clearly contrary to the Action's assertion that "there is no reason to believe that the teachings of the patent, specifically which compounds are suitable for increasing stability of a lyophilized protein, are so limited as to only apply to this one particular protein."

Furthermore, YAMAHIRA fails to disclose the use of arginine, the use of arginine plus HSA, or the use of any other polar amino acid as a broadly applicable stabilizing agent with respect to any lyophilized protein. In the absence of such a generic teaching, it is incumbent upon the Office to provide a specific reason why YAMAHIRA's teachings with respect to urokinase are applicable to HGF. Yet the Office has failed to establish a nexus between urokinase and HGF such that one of ordinary skill in the art would have been motivated to combine the teachings of TANAKA with those of YAMAHIRA. Accordingly, Applicant submits that one of ordinary skill in the art would not have been motivated to combine the

teachings of TANAKA and YAMAHIRA for at least two reasons. First, YAMAHIRA's teachings appear to apply specifically to the preparation of a stable *urokinase* injection. Second, in the absence of a general teaching with respect to any lyophilized protein, the Office has otherwise failed to establish a nexus between urokinase and HGF.

With regard to the Office's assertions regarding the concentration of HGF in the aqueous solution from which the claimed invention is prepared as compared to TANAKA, Applicant submits that the Office Action incorrectly states the legal standard upon which product-by-process limitations are given patentable weight: the question is whether the *process* limitations result in a materially different *product*. Under the Office's mistaken standard, Applicant would have to prove patentability in order for a process limitation to be given any patentable weight – this is clearly illogical and incorrect.

As the specification clearly explains, by way of background information and Examples (exemplary of the invention as well as comparative), the concentration of HGF materially impacts the performance of the end product. In particular, the specification provides evidence (summarized in Tables 7 and 8 on pages 24 – 25) that – absent the claimed stabilizing agents – concentrations of less than 5 mg/mL produce aggregates in an accelerated manner. Accordingly, evidence is present which indicates that that a product made from a higher concentration of HGF is distinct, i.e., that the process limitations result in a materially different product.

In particular, as described in Test Example 4 and Table 8 on pages 23 – 25 of the instant specification, when compositions such as those taught by TANAKA comprising glycine or alanine as stabilizers were prepared in compositions wherein HGF concentration was low, i.e., lower than 5 mg/mL HGF, it was found that aggregate formation was accelerated and storage stability was lowered (see also, e.g., Examples 5 and 6 at page 12 of the specification). From

these comparative experimental results it can be understood that a lower concentration of HGF gave aggregation of HGF and reduced stability when glycine (Example 5) or alanine (Example 6) were used as a stabilizer.

Applicant also submits that the instant specification makes clear that the present invention represents an improvement over the HGF composition taught in TANAKA, at least insofar as (1) TANAKA's lyophilized preparation of HGF was prepared at a high concentration, (2) TANAKA's use of citric acid as a buffering agent meant the re-dissolved preparation was acidic, and (3) the resulting solution taught by TANAKA had a high osmotic pressure, which causes problems of pain at administration by injection, or inflammatory rejection and hemolysis at the site of administration (see specification at page 2, second full paragraph).

Applicant further submits that the Office has failed to establish a *prima facie* case of obviousness, at least because the Office has failed to show that the cited art, either alone or in combination would yield the invention as claimed. Specifically, neither TANAKA nor YAMAHIRA, either alone or in combination, teach "[a] lyophilized preparation comprising a hepatocyte growth factor, a stabilizing agent comprising arginine, lysine, histidine, glutamine, proline, glutamic acid, or aspartic acid, or a pharmacologically acceptable salt thereof, for preventing formation of an aggregate of the hepatocyte growth factor, sodium chloride, and a buffering agent, which is prepared from an aqueous solution containing the hepatocyte growth factor at a concentration lower than 5 mg/mL."

Based at least on the foregoing, Applicant submits that the claimed invention is not fairly suggested or anticipated by TANAKA and/or YAMAHIRA, either alone or in combination. Accordingly, Applicant respectfully requests reconsideration of the rejection under 35 U.S.C. § 103(a) and withdrawal of the same.

CONCLUSION

In view of the foregoing remarks, the Examiner is respectfully requested to reconsider and withdraw the rejections of record, and allow each of the pending claims. Applicant therefore respectfully requests that an early indication of allowance of the application be indicated by the mailing of the Notices of Allowance and Allowability.

Should the Examiner have any questions regarding this application, the Examiner is invited to contact the undersigned at the below-listed telephone number.

Respectfully Submitted,
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